Synthesis of Racemic and Enantiopure Samples of Zearalenone

by Scotty L. Blechman

B.S. in Biochemistry, Northeastern University

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Thesis directed by

George A. O’Doherty
Professor of Chemistry and Chemical Biology
Dedication

To fellow members of the LGBTQA+ community in STEM fields who work towards a better environment for aspiring queer scientists.
Acknowledgements

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Abstract of Thesis

Herein, synthesis of the resorcylic acid lactone (RAL) zearalenone is investigated. As an excellent model compound, zearalenone has been synthesized over 20 times, but the proposed route would be the first instance of a high-yield *de novo* asymmetric synthesis of zearalenone without use of kinetic resolution or enzymatic catalysis. Due to time constraints, the synthesis has not yet been completed, but early results are promising. The synthesis also features a novel tandem gold(I)-catalyzed hydroalkoxylation and Claisen rearrangement, the conditions of which are currently being optimized.
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List of Abbreviations

9-BBN  9-borabicyclo[3.3.1]nonane
Ac     acetyl
acac   acetylacetonate
AIBN   azobisisobutyronitrile
amt.   amount
aq.    aqueous
atm    atmospheres
BAIB   bis(acetoxy)iodobenzene
BINAP  (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
BTA    1H-benzotriazole
Bz     benzoyl
CAL-B  Candida antarctica lipase B
CDI    1,1′-carbonyldiimidazole
COD    1,5-cyclooctadiene
Cp     cyclopentadienyl
CTAB   cetyltrimethylammonium bromide
Cy     cyclohexyl
δ      chemical shift, delta
d      doublet
dba    trans,trans-dibenzylideneacetone
DBU    1,8-diazabicyclo[5.4.0]undec-7-ene
DCC    N,N′-dicyclohexylcarbodiimide
DCM  dichloromethane  
DEAD diethyl azodicarboxylate  
DEM diethyl malonate  
den. density  
DEP diethyl phthalate  
DHP 3,4-dihydro-2H-pyran  
DIBAL-H diisobutylaluminum hydride  
DIPEA N,N-diisopropylethylamine  
DMA N,N-dimethylaniline  
DMAP 4-(dimethylamino)pyridine  
DMC dimethyl carbonate  
DMP Dess-Martin periodinane  
DMS dimethyl sulfide  
DMSO dimethyl sulfoxide  
DPEN 1,2-diphenyl-1,2-ethylenediamine  
DPS 2,2’-dipyridyldisulfide  
EA ethyl acetate  
EDCI 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide  
ent enantiomer [of]  
eq equivalents  
Et ethyl  
g grams  
h hours
<table>
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<tr>
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<th>Full Form</th>
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<tr>
<td>hex</td>
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</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazane</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>hv</td>
<td>photo-catalyzed</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>imid.</td>
<td>1H-imidazole</td>
</tr>
<tr>
<td>J</td>
<td>spin-spin coupling constant</td>
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<tr>
<td>KAPA</td>
<td>potassium 3-aminopropylamide</td>
</tr>
<tr>
<td>L</td>
<td>liters</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LTBA</td>
<td>lithium tri-tert-butoxyaluminum hydride</td>
</tr>
<tr>
<td>m</td>
<td>milli, multiplet</td>
</tr>
<tr>
<td>M</td>
<td>molar (moles/liter)</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MEM</td>
<td>β-methoxyethoxymethyl</td>
</tr>
<tr>
<td>Mes</td>
<td>mesitylene</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>mol</td>
<td>moles</td>
</tr>
<tr>
<td>MPTS</td>
<td>methyl p-tolyl sulfoxide</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
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<tr>
<td>MVK</td>
<td>methyl vinyl ketone (but-3-en-2-one)</td>
</tr>
<tr>
<td>MW</td>
<td>molecular weight</td>
</tr>
<tr>
<td>N</td>
<td>normal (equivalents/liter)</td>
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<tr>
<td>NADP⁺</td>
<td>nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-butyl</td>
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<td>NCS</td>
<td>N-chlorosuccinimide</td>
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<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>p</td>
<td>pentet</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>p-Ts</td>
<td>para-toluenesulfonyl</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quadruplet/quartet</td>
</tr>
<tr>
<td>rac</td>
<td>racemic</td>
</tr>
<tr>
<td>RAL</td>
<td>resorcylic acid lactone</td>
</tr>
<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
</tr>
<tr>
<td>Red-Al</td>
<td>sodium bis(2-methoxyethoxy)aluminum dihydride</td>
</tr>
<tr>
<td>Rf</td>
<td>ratio to front</td>
</tr>
<tr>
<td>rt, RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
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S/C  substrate/catalyst (ratio)
t  triplet
TAA  tert-amyl alcohol
TBADH  *Thermoanaerobium brockii* alcohol dehydrogenase
TBAF  tetra-<i>n</i>-butylammonium fluoride
TBAI  tetra-<i>n</i>-butylammonium iodide
TBDPS  tert-butylidiphenylsilyl
TBS  tert-butylidimethylsilyl
<i>t</i>-Bu  tert-butyl
TEMPO  (2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA  trifluoroacetic acid, trifluoroacetate
TFAA  trifluoroacetic anhydride
THF  tetrahydrofuran
THP  2-tetrahydropyranyl
Tf  triflyl (trifluoromethanesulfonyl)
TFP  tri(2-furyl)phosphine
TLC  thin-layer chromatography
TMS  trimethylsilyl
Tol.  toluene
Ts  *para*-toluenesulfonyl
Vol.  volume
Introduction

Zearalenone, a potent estrogen receptor agonist and East Asian crop toxicity factor, is a 14-membered benzo-fused macrolactone from the resorcylic acid lactone (RAL) family. It has shown a variety of intriguing biological activities, including genotoxicity, pro-apoptotic effects, and lipid peroxidation, and it also has applications in veterinary medicine and livestock growth. As a chiral, functionalized macrolactone, zearalenone has served as an excellent model compound for investigating new macrolactonization methods and other types of macrocyclic ring closure, having been synthesized over 20 times since 1957. However, no asymmetric synthesis to date has achieved a high overall yield with the use of only non-enzymatic asymmetric catalysis, rather than an enzyme, a chiral auxiliary, or kinetic resolution. Herein, a highly versatile “Noyori-zipper” reaction sequence consisting of the Noyori asymmetric hydrogenation and alkyne zipper reaction is used to form the foundation of the optically enriched macrolactone chain. From the terminal alkynol product, a tandem gold(I)-catalyzed hydroalkoxylation and Claisen rearrangement is used to form the macrolactone precursor, and from here requires only another 5 steps to reach the natural product. A shorter, racemic approach from a commercially available ω-hydroxy alkyne is also presented. Due to time constraints, the synthesis has not yet been completed, but the early steps show promising results. Future plans include biological assays of the natural product, as well as synthetic modifications including glycosylation and isomerization.
Chapter 1:

Background and Previous Syntheses of Zearalenone

1.1 Introduction to Zearalenone and Other Resorcylic Acid Lactones

Zearalenone, a benzo-fused macrocycle first isolated from the fungus Gibberella zeae (Fusarium graminearum) in 1962, is a potent estrogen receptor agonist and a member of a family of similar natural products known as resorcylic acid lactones (RALs). The structure of zearalenone (F1.1) was first elucidated in 1966 by Urry et al., and the compound was later isolated from several other Fusarium species. Zearalenone (also known as F-2 mycotoxin) is a significant dietary risk factor due to its occurrence, along with its “masked” glycoside derivatives, in cereal crops such as wheat, corn, and rice. Its alcohol derivative zeranol (F1.4) is used as an antibiotic growth hormone in cattle as well as an anabolic drug in veterinary medicine. Zearalenone has shown a wide variety of intriguing biological activities, including genotoxicity, pro-apoptotic effects, estrogen receptor agonism and lipid peroxidation. Zearalenone and its derivatives (Fig. 1) are all promising compounds for both synthetic and biological studies, and in particular the reduced analog zeranol has found commercial applications in veterinary medicine and livestock growth.

![Zearalenone and its derivatives](image)

Figure 1. Zearalenone and some of its derivatives.

1.2 Previous Approaches to Zearalenone Synthesis
1.2.1 First Total Syntheses of Zearalenone

The first total synthesis of zearalenone was reported by Wendler in 1967. The aromatic component of the molecule was formed from 3,5-dimethoxyphthalic anhydride (1.5), which was synthesized according to earlier procedures from Brockmann’s group (Scheme 1). Starting with α-resorcylic acid (1.1), the hydroxy groups were protected by methylation with sodium hydroxide and dimethyl sulfate, while the acid was esterified via Fischer esterification in methanol to give methyl ester 1.2. Next, chloral hydrate was used to annulate the molecule between the ester and the ortho position according to Fritsch’s protocol. The trichloromethyl group was converted to a carboxylic acid using potassium hydroxide to form lactone 1.3. Oxidative decarboxylation was then accomplished by treatment with diethyl phthalate (DEP), and the 5-member lactone was subsequently opened with sodium hydroxide and potassium permanganate to afford dicarboxylic acid 1.4. The corresponding anhydride 1.5 was obtained after the addition of acetic anhydride. Finally, the Wendler group obtained the aromatic fragment 1.6 by selective reduction with lithium tri-tert-butoxyaluminum hydride (LTBA).

Scheme 1. Aromatic fragment synthesized by Wendler’s group.

With the aromatic fragment 1.6 in hand, Wendler then prepared the aliphatic component 2.4. This began with the synthesis of 5-hexalactone 2.3 by sodium borohydride reduction of 5-oxoheanoic acid (2.1) and subsequent cyclization of the alcohol (±)-2.1 in acid, then a Grignard reaction between 2.3 and pent-4-enylmagnesium bromide (Scheme 2). The product of the
Grignard addition was then treated with methanolic hydrogen chloride to give the methyl mixed ketal 2.4. The methylidene group of 2.4 was cleaved by ozonolysis, and the resulting aldehyde was reduced with sodium borohydride, giving an unstable alcohol. The crude primary alcohol was promptly converted to tosylate 2.5 with $p$-toluenesulfonyl chloride in pyridine. The tosylate 2.5 was treated with sodium bromide to afford 2.6, and then treated with triphenylphosphine to provide the Wittig salt 2.7. The Wittig salt was combined with 2.10 (1.6 in Scheme 1) in the presence of dimsyl sodium; however, as is common for Wittig reactions with unstabilized ylides, the selectivity was poor, and this severely hurt the yield – 55% total yield with a 13:12 trans:cis ratio, only a 29% yield of the desired product 2.8 after acid-opening of the 6-membered ring. Direct cyclization with trifluoroacetic anhydride closed the macrolactone ring, though in low yield (10%), and methyl groups were easily removed with boron tribromide to afford rac-zearalenone (2.9) in a total of 12 longest-linear steps. The overall yield from $\alpha$-resorcylic acid was 0.08%, leaving significant room for improvement.

Scheme 2. Completion of 1957 Wendler synthesis.
In 1958, Wendler’s group published a more detailed paper on their racemic zearalenone synthesis. In this approach, they were able to assign absolute configuration of zearalenone (Scheme 3). They found that one of the methyl groups could be selectively cleaved on the methyl-protected zearalenone (±)-3.4 to give the mono-methylated (±)-3.5. The selective cleavage was exploited for resolution of enantiomers. This was accomplished by the conversion of the phenol group in 3.5 to the mixture of diastereomeric menthoxycetate derivatives 3.6. The mixture of diastereomers was separated. The more abundant diastereomer was then converted into (−)-3.5 by saponification and deprotection of the remaining methyl group using boron tribromide to give optically pure (−)-zearalenone (3.7). The optically pure material was remethylated, the ketone was protected with ethylene glycol, and the olefin was hydrogenated to give 3.8. After opening the lactone with sodium hydroxide and esterification with diazomethane, alcohol 3.9 was treated with racemic α-phenylbutyric anhydride according to Horeau’s
methodology\textsuperscript{13} to determine stereochemistry by preferential reactivity. The majority of the recovered free α-phenylbutyric acid was levorotatory, so Wendler’s group determined the configuration of (−)-zearalenone to be (S).

**Scheme 4. Cross’s 1968 approach to the aliphatic part of zearalenone.**

Cross’s group also published a total synthesis of zearalenone in 1968.\textsuperscript{14} The route was very similar to Wendler’s route, with some differences in the synthesis of the aliphatic part of the molecule (Scheme 4) and in the macrolactonization approach (Scheme 5). The aliphatic fragment started from 5-hexen-2-one (4.1). Sodium hydride facilitated the carboxyethylation of 4.1 with diethyl carbonate at the α’-carbonyl position. The carbon chain was then further extended by the Michael addition of nucleophilic enolate 4.2 to methyl vinyl ketone (MVK) to give the racemic methyl ketone 4.3. The tricarbonyl 4.3 was converted to diketone 4.6 by a three-step ester hydrolysis and decarboxylation reaction sequence. This involved ketal formation (4.3 to 4.4), base-promoted ester hydrolysis, and then an acid-catalyzed mixed ketal hydrolysis and decarboxylation to form 4.6. After protecting both ketones in 4.7 with ethylene ketal, Cross’s group used a hydroboration-oxidation to give anti-Markovnikov alcohol 4.8, which was then
tosylated with \( p \)-tosyl chloride, brominated with lithium bromide, and treated with triphenylphosphine to form Wittig salt 4.11.

Cross’s group utilized a similar Wittig olefination to couple 5.2 (4.11 in Scheme 4) with the aromatic fragment 5.1 to give 5.3, which then required 6 more steps to reach the macrolactone final product 5.5. Because of the required protecting group manipulations, this route required 4 extra steps after the Wittig olefination. The \( t \)-amyl alcohol macrolactonization also suffered from a similarly low yield (8%) to Wendler’s TFAA method. Cross’s synthesis was completed in a total of 17 longest-linear steps. The Cross route prepared zearalenone in a 0.59% overall yield, which was an improvement over Wendler’s synthesis (0.08%).

Scheme 5. Completion of Cross’s zearalenone synthesis.

1.2.2 Development of Novel Macrolactonization Methods

In 1974, Corey and Nicolaou reported the discovery of a novel macrolactonization method via \( \omega \)-hydroxy-2-pyridinethiol esters (6.4). The method, aptly named the Corey-Nicolaou macrolactonization, is a one-pot 2-step process carried out by adding triphenylphosphine and 2,2’-dipyridyldisulfide (6.1, DPS) to the \( \omega \)-hydroxy acid 6.2 (Scheme 6). In the first step, after cleavage of the disulfide bond by triphenylphosphine (6.2 to 6.3), the acid is converted to a 2-pyridinethiol ester (6.3 to 6.4). The basic pyridine group then facilitates
macrolactonization between the alcohol and mixed anhydride to generate the lactone 6.6. The transformation was best applied at reflux in dry xylene, and took between 30 and 50 hours total. Corey and Nicolaou reported that this macrolactonization method gave yields between 64% and 88% by GLC for 7-, 12-, 13-, 14-, and 16-membered macrolactones, a massive improvement from the macrolactonizations used by Wendler and Cross. When Corey and Nicolaou directly applied this method to zearalenone (Scheme 7), they produced the 14-membered zearalenone ring in 75% yield.

**Scheme 6. Mechanism of the Corey-Nicolaou macrolactonization.**

The following year, Masamune et al. also published a new strategy for macrolactonization. The method is based on the affinity of electrophilic mercury(II) ions for bivalent sulfur. After converting the seco-acid derivative 8.1 of a macrolactone to the
corresponding \(S-t\)-butyl thioester 8.2, mercury(II) ions promote the intramolecular transesterification. Masamune’s group illustrated this method with the Cross’s protected seco-acid derivative 8.1. Using thallous 2-methylpropane-2-thiolate (Scheme 8), Masamune produced thioester 8.2 in quantitative yield. Treating the crude thioester with mercury(II) trifluoroacetate induced a macrolactonization in only 5 minutes at RT, and afforded the product in over 90% yield. This macrolactonization occurred in a higher yield and significantly shorter reaction time compared to the Corey-Nicolaou method. Because mercury reagents have toxicity and environmental concerns, Masamune’s group showed in 1977 that the same macrolactonization method could be accomplished in high yield with silver(I), copper(I), and copper(II) compounds in place of mercury(II) reagents. These new methodologies discovered by Corey/Nicolaou and Masamune et al. transformed the field of macrolactone synthesis, being among the first examples of consistently high-yield macrolactonizations.

Scheme 8. Masamune macrolactonization as applied to zearalenone.

1.2.3 Intramolecular Alkylations and Other Improvements

Between 1979 and 1982, Tsuji’s group at Tokyo Institute of Technology made several innovative contributions to the synthesis of zearalenone. In their 1979 synthesis of racemic dimethylzearalenone, they sought to address the issues with the Wittig reaction in the previous syntheses. Tsuji’s group instead utilized an intramolecular alkylation approach to form the olefin. A benzylic phenyl thioether group served a double role of carbanion stabilization in the ring-closing alkylation (10.12 to 10.13), and, via sulfoxide elimination, \textit{trans}-olefin selectivity (10.13 to 10.14).
Scheme 9. Synthesis of aromatic fragment according to Tsuji 1978.

The aromatic fragment of the molecule was synthesized according to Tsuji’s 1978 protocol (Scheme 9). The methyl ester of orsellinic acid (9.3) was formed by reacting methyl acetoacetate (9.1) with diketene (9.2) in the presence of sodium hydride. Methylation with methyl iodide achieved only the monomethylated product 9.4, which was then subjected to radical allylic bromination affording 9.5. After methylation of the other hydroxyl group with diazomethane, the allylic bromide was replaced with a thiophenol group to give thioether 9.6. A simple hydrolysis of the methyl ester with potassium hydroxide formed the free acid 9.7. An unspecified method converted this acid to the respective acid chloride 9.8.

Tsuji’s group then set out to synthesize the aliphatic fragment (Scheme 10). The starting material 10.3 was synthesized by a palladium-catalyzed dimerization of butadiene (10.1) in acetic acid to form 10.2, then hydrolysis of the acetate group gave 10.3. The hydroxyl group of the starting material was oxidized to form α,β-unsaturated ketone 10.4 by a gas-phase dehydrogenation, catalyzed by a copper/zinc alloy. This Michael acceptor was then reacted with diethyl malonate (DEM) in the presence of sodium ethoxide to afford diester 10.5. An S_N2 hydrolysis with sodium iodide and water and decarboxylation gave 10.6. The ketone was then protected as an ethylene ketal (10.7), and the ester was reduced to an alcohol which was tosylated to give 10.8. A Wacker oxidation converted the terminal alkene into methyl ketone.
10.9. The ketone was reduced with sodium borohydride, and the tosylate was then treated with sodium iodide in acetone to give iodide 10.10.

Scheme 10. Tsuji’s 1979 synthesis of dimethylzearalenone.

With the aliphatic fragment (10.10) in hand, Tsuji’s group coupled it with the aromatic fragment (10.11; 9.8 in Scheme 9) to form ester 10.12 in 90% yield. An intramolecular alkylation was used for the macrocyclic ring-closing step, which was accomplished with KHMDS as a base to give 10.13 in 85% yield. In terms of yield, the route rivals those of the Corey-Nicolau and Masamune methods. The thiophenyl group was oxidized, and the resulting sulfoxide was eliminated to form the trans olefin in 80% yield. Removing the ethylene ketal with para-toluenesulfonic acid afforded the product, dimethylzearalenone (10.14), in 5.8% overall yield from 10.3, nearly 10-fold higher than the yield from Cross’s group (albeit before removing the methyl groups).
Tsuji’s group published a formal synthesis of zearalenone (Scheme 11) the following year,21 this time using α-resorcylic acid (11.1) as the aromatic starting material. The acid was converted into dimethyl-α-resorcylic acid methyl ester (11.2) by one of the previously disclosed methods (diazomethane or methyl iodide and base). A radical bromination and ester reduction gave bromide 11.3, which was then converted to iodide 11.4 via metalaation with n-butyl lithium and an iodine quench. Treatment with thionyl chloride converted the hydroxyl group into a benzyl chloride, which was then displaced with thiophenol anion providing the desired aryl iodide substrate (11.5) for a novel palladium-catalyzed carbylation reaction. The two fragments were brought together with carbylation/ester formation with carbon monoxide and 11.6 (10.12 in Scheme 10) gave 11.7 which could be converted into dimethylzearalenone via the intramolecular alkylation route published the previous year. This carbylation had previously only been applied to primary alcohols which were used in large excess. In contrast, Tsuji’s group was able to use only 2 equivalents of a secondary alcohol to give 11.7 in 70% yield. Furthermore, the method was selectively reactive toward the aryl sp² iodide of 11.5 over the aliphatic sp³ iodide in 11.6.


Tsuji’s group reported another total synthesis of dimethylzearalenone in Tetrahedron Lett. 1981.22 The synthetic route (Scheme 12) features another intramolecular alkylation, this
time in a reaction that produced the carbonyl carbon of the product. To this end, the previously used iodide 12.1 (11.5) was carbonylated with 12.2 to give 12.3, which was then alkylated with 12.4 to form 12.5. Building on their previous approach, an oxidation/elimination of the thiophenyl group to form the olefin, and subsequent deprotection gave the aldehyde 12.6. The alcohol was tosylated (12.6 to 12.7), and the aldehyde was converted into protected cyanohydrin 12.8 by sequential treatment with sodium bisulfite, sodium cyanide, and ethyl vinyl ether. The intramolecular alkylation with NaHMDS proceeded in 85% yield. Only two more steps were necessary to reach the product dimethylzearalenone (12.11). Deprotection with aqueous hydrochloric acid gave the naked cyanohydrin 12.10, which after washing with 5% potassium hydroxide gave the corresponding ketone, dimethylzearalenone.

**Scheme 12. Cyclization via protected cyanohydrin (Tsuji 1981).**
Scheme 13. Further investigation of the dianion effect by Tsuji’s group.

In 1982, Tsuji’s group published in *Tetrahedron Lett.* a study of the scope of the intramolecular cyclization to form dimethylzearalenone. This revised route mirrors his previous approach but switches the positions of the iodide and cyanohydrin. The route started with aryl iodide 13.1 which was carbonylated with 13.2 to form 13.3. Alkylation at the benzylic position of 13.3 with 13.4 yielded 13.5. The chloride 13.5 was converted into 13.6 via a 5-step sequence which includes a Finkelstein reaction, removal of the alcohol protecting group, oxidation with chromium trioxide, HCN addition, and ethyl vinyl ether protection. Tsuji posits that the benzylic and α-cyano carbanions serve multiple purposes; first, the thiophenol group on the benzylic carbanion limits the acyclic conformation, which facilitates cyclization. The thiophenol and carbanion also protect the neighboring ester group both sterically and electronically, preventing nucleophilic attack. Lastly, the two carbanions cause intermolecular repulsion, preventing dimerization and instead encouraging the intramolecular cyclization. The cyclization with sodium hexamethyldisilazane proceeded in high yield to give the macrolactone product 13.7, which after acid deprotection of the cyanohydrin, conversion to the ketone in base, and periodate oxidation and elimination of the thiophenyl ether yielded dimethylzearalenone (13.8).
1.2.4 Optically Active Zearalenone via Radical Intermediate

The next synthesis of zearalenone (Scheme 14) was reported by Pattenden and Hitchcock in 1990, and featured a radical macrolactonization.\textsuperscript{23,24} The synthesis utilized an enantiopure starting material, the naturally occurring (S)-parasorbic acid (14.6), to make an optically pure sample of (S)-(−)-zearalenone (14.19). The aromatic fragment was synthesized from dimethylorsellinic acid (14.1), which was converted into thiophenyl 14.2 in accordance with Tsuji’s strategy for double bond installation. The thiophenyl 14.2 was deprotonated with KHMDS and alkylated with ethyl iodide to give the α-ethyl thiophenol 14.3. Periodate was used to oxidize the sulfide, and heat was used to induce an elimination to form the double bond. Ester saponification with KOH-DMSO afforded 14.4 in 75% overall yield, and subsequent treatment with oxalyl chloride gave acid chloride 14.5. Pattenden and Hitchcock then turned to the enantiopure parasorbic acid (14.10). Double bond hydrogenation and reduction of the lactone afforded the corresponding lactol 14.11. Treatment with propane-1,2-dithiol in the presence of boron trifluoride opened the lactol and protected the resulting aldehyde as a dithiane (14.12). The hydroxy dithiane was then coupled with acid chloride 14.5 to form ester 14.13. After a mercury(II) deprotection of the dithiane, the resulting aldehyde 14.14 was reacted with a vinyl Grignard reagent, and the resulting racemic allylic alcohol was oxidized to ketone 14.15. Radical bromination at the allylic position gave allylic bromide 14.16, the precursor for the radical ring closure. The 14-\textit{endo}-trig cyclization gave (S)-dimethylzearalenone (14.18) in 55% yield via allylic radical intermediate 14.17. Deprotection of the hydroxyl groups with boron tribromide yielded (S)-zearalenone (14.19) in 36% yield.
1.2.5 Utilizing Stille Coupling

In 1991, Kalivretenos, Stille (posthumous), and Hegedus reported another synthesis of optically pure (S)-zearalenone in *J. Org. Chem*. Optical purity was again achieved by the use of an enantiopure starting material, (R)-propylene oxide (15.6). The cyclization of the macrolactone was accomplished via a palladium-catalyzed Stille coupling, the first use of the Stille coupling
for synthesis of zearalenone. To form the Stille reagent, terminal alkyne 5-hexyn-1-ol (15.1) was protected as silyl ether 15.2 and converted to vinyl iodide 15.3 by use of the Schwartz reagent. Treatment of 15.3 with n-butyllithium followed by tri-n-butyltin chloride replaced the iodide with a tri-n-butylstannyl group, and subsequent deprotection of the TBS group gave free alcohol 15.4. The alcohol was oxidized to aldehyde 15.5 by Corey-Kim oxidation.

**Scheme 15. Hegedus’s (S)-zearalenone synthesis featuring Pd-catalyzed Stille coupling.**

With the vinyl tin fragment 15.5 in hand, Hegedus moved onto the chiral part of the molecule. (R)-propylene oxide (15.6) was opened by the addition of a vinyl cuprate intermediate to give 15.7. Protection of alcohol 15.7 followed by hydroboration-oxidation gave primary
alcohol 15.8 which was subjected to Appel bromination yielding bromide 15.9. The bromide was converted into a Grignard reagent which added to aldehyde 15.5 to give alcohol 15.10. After oxidation of alcohol 15.10 back to a ketone, the TBS group was deprotected to afford Stille reagent 15.11. The aromatic moiety was synthesized from β-resorcylic acid methyl ester 15.12. The two phenols were protected as silyl ethers 15.13 while the methyl ester was converted into a diethyl amide 15.14. Treating 15.14 with tert-butyllithium and then iodine chloride selectively iodinated the ortho position to an amide. The iodoamide intermediate was then converted back to the methyl ester and the phenols were deprotected to yield 15.15. The phenols were then protected as MEM ethers and the ester was hydrolyzed to form acid 15.16. The tributylstannyl-containing side chain 15.11 was coupled with acid 15.16 by a Mitsunobu reaction to afford the Stille macrolactonization precursor 15.17. The cyclization via Stille coupling worked best with catalytic tetrakis(triphenylphosphine)palladium(0) in toluene at reflux, affording macrolactone 15.18 in 54% yield. The MEM groups were removed with 5% aqueous hydrogen chloride in THF, affording the product (S)-(−)-zearalenone (15.19). The synthesis of zearalenone occurred in 7.6% overall yield from (R)-propylene oxide.

1.2.6 Stereoselectivity via Chiral Auxiliary and Enzyme Catalysis

The first chiral auxiliary synthesis of zearalenone was reported by Solladié et al. in J. Org. Chem. 1991. The synthesis used only achiral starting materials – methyl 4-iodobutyrate (16.1), orcinol (16.4), and glutaric anhydride (17.1) – but the chiral auxiliary (R)-methyl p-tolyl sulfoxide ((R)-MPTS) was necessary for this route. The iodide 16.1 was substituted with a sulfonyl group, and the methyl ester was reduced to primary alcohol 16.2 with LiAlH₄. The alcohol was then converted to iodide 16.3 using iodine, imidazole, and triphenylphosphine. Solladié then subjected orcinol (16.4) to a Gattermann formylation and subsequently protected
the synthesis, aromatic fragment 16.5. The aldehyde was converted into the corresponding carboxylic acid by a Pinnick oxidation, then treated with dimethyl sulfate to give methyl ester 16.6. Sulfinylation at the benzylic position gave the p-tolyl sulfoxide 16.7, which was reduced with boron trifluoride and sodium iodide to p-tolyl sulfide 16.8. The sulfide was alkylated with previously prepared iodide 16.3 yielding 16.9, and the sulfide was re-oxidized to sulfoxide 16.10 with m-CPBA. Thermal elimination of the sulfoxide group gave trans olefin 16.11.

Scheme 16. Solladié’s approach to the resorcylic acid fragment.

Turning to the chiral fragment of the molecule, Solladié started with the achiral glutaric anhydride (17.1) and opened it with the lithium anion of the chiral auxiliary, (R)-MPTS. Treatment of the resulting acid with diazomethane gave methyl ester 17.2. The β-ketosulfoxide was diastereoselectively reduced with DIBAL-H via a zinc chelate to afford the (R) alcohol 17.3 in over 98% diastereomeric excess. The alcohol was protected as a TBS group, and the chiral auxiliary was removed with Raney nickel to give optically pure building block 17.4. To complete the synthesis, aromatic fragment 18.1 was combined with protected enantiopure alcohol 18.2 in
the presence of lithium hexamethyldisilazane to give the ketone 18.3. The p-tosyl group was removed with a sodium/mercury amalgam, and the ketone 18.4 was protected to form dithiane 18.5. Saponification of the methyl ester was followed by phosphoric acid mixed anhydride mediated macrolactonization. The macrolactonization procedure was developed by Masamune. Deprotection of the cyclized product 18.6 gave the final product, (S)-dimethylzearalenone (18.7), in over 95% enantiomeric excess and 7.6% overall yield from orcinol, a similar overall yield as was achieved by Hegedus.

Scheme 17. Solladić’s chiral auxiliary approach to the chiral side-chain.

Scheme 18. Completion of Solladić’s asymmetric synthesis.

Later in 1991, the Keinan group at Technion presented a de novo asymmetric approach to the aliphatic portion of (S)-zearalenone. Their synthesis started from ethyl acetoacetate (19.1).
The ketone was protected as an ethylene ketal, then the ester was reduced to primary alcohol 19.2 with LiAlH₄. The alcohol was converted into the corresponding iodide 19.3 via a tosylate intermediate. Next, hex-5-en-2-one (19.4) was converted into methyl ester 19.5 and coupled with 19.3 via decarboxylation to give 1,3-diketone 19.6. The diketone was both regioselectively and stereoselectively reduced to secondary alcohol 19.7 by the enzyme alcohol dehydrogenase TBADH with cofactor NADP⁺.

**Scheme 19. Enzyme-catalyzed asymmetric reduction by Keinan's group.**
After protecting group manipulations, the group completed their synthesis via Tsuji’s intramolecular alkylation route with slight modifications. Aromatic fragment 19.15 was prepared in four steps starting with dimerization-cyclization of the dienolate of methyl acetoacetate (19.11) with sodium hydride and \( n \)-BuLi, then methylation of the resulting 2,4-diphenol 19.12. Sulfinylation of the methylated product 19.13 and hydrolysis of the resulting ester 19.14 gave 19.15. The aromatic fragment 19.15 was combined with aliphatic fragment 19.10 in the presence of tributylamine and 2-chloro-\( N \)-methylpyridinium chloride (19.16) to afford ester 19.17. A 3-step sequence consisting of hydroboration-oxidation, tosylation, and iodination of ester 19.17 gave iodide 19.18. Macrocyclic precursor 19.18 was cyclized by Tsuji’s 1979 method using NaHMDS as a base to give 19.19. The thiophenyl group was eliminated to olefin 19.20, and deprotection of the ethylene ketal gave ketone 19.21. Deprotection of the methyl ethers by Wendler’s method gave the product, (\( S \))-\( (–) \)-zearalenone (19.22).

### 1.2.7 Solid Phase Synthesis

Nicolaou’s group published another synthesis of zearalenone in 1998.\(^28\) The Nicolaou route was a solid-phase synthesis on Merrifield polystyrene resin (20.1). The synthesis started with an oxidation of the Merrifield resin followed by a Wittig olefination to form the vinyl group of 20.2. The vinyl group was stannylated to afford polystyrene-di-\( n \)-butyltin chloride (PBTC, 20.3), which was dehalogenated with lithium borohydride to polystyrene-di-\( n \)-butyltin hydride (PBTH, 20.4). Organolithium reagent 20.5 was then added to the resin 20.4 forming TBS-protected alcohol 20.6, which upon deprotection and Corey-Kim oxidation became aldehyde 20.7. The chain was further extended by a Grignard addition of 20.8 yielding alcohol 20.9 as a mixture of diastereomers. The secondary alcohol which was oxidized to ketone 20.10 with Corey-Kim oxidation. Deprotection of the silyl ether gave free secondary alcohol 20.11.
Building upon the Hegedus approach, the cyclization precursor 20.12 was prepared by a Mitsunobu reaction and a Stille coupling which also released the cyclized product from the resin. The cyclization-release selectively formed the desired E-olefin 20.13, with the Z-isomer not being observed at all. Deprotection in acid afforded the product, (S)-zearalenone (20.14).

**Scheme 20. Solid phase synthesis on polystyrene resin by Nicolaou’s group.**

1.2.8 Kinetic Resolution and Grubbs Metathesis

In *J. Org. Chem.* (2000), the Fürstner group published a new synthesis of (S)-zearalenone (Scheme 21). The synthesis achieved optical purity via Jacobsen’s kinetic resolution methodology. The aromatic fragment started from 3,5-dimethoxyphenol (21.1), which was carboxylated utilizing a Kolbe-Schmitt reaction, as in Fürstner’s 1999 zeranol synthesis, to give phenol 21.2. Fürstner performed a Jacobsen kinetic resolution of racemic propylene oxide (21.4) using Jacobsen catalyst 21.3. Though limited to a 50% yield due to the nature of chiral resolution, a 44% yield was achievable with over 98% enantiomeric excess. The optically pure
sample of (R)-21.4 was alkylated with a copper-catalyzed vinylmagnesium bromide ring opening, and the resulting alcohol 21.5 was protected as TBS ether 21.6. Schwartz’s reagent was used for a regioselective hydrozirconation, and subsequent cyanation by treatment with tert-butyl cyanide and iodine gave nitrile 21.7. Another Grignard addition was utilized to add the 4-pentenyl group. The resulting ketone 21.8 was protected as an ethylene ketal, and the silyl ether was deprotected by TBAF to give 21.9.

Scheme 21. Synthesis by Fürstner’s group in 2000 with Grubbs RCM.

This chiral fragment 21.9 was coupled with aromatic fragment 21.2 by Mitsunobu reaction in an excellent yield of 88%. After converting the coupled product 21.10 into triflate 21.11, a Heck
reaction was used to convert the triflate into an ethylene group giving macrocyclization precursor 21.12. The diene was readily cyclized to 21.14 by Grubbs ring-closing metathesis with 2nd generation Grubbs catalyst 21.13. Two final deprotection steps gave the product 21.15, (S)-zearalenone, though the deprotection of the methyl ethers suffered from the low yield of 55%. This synthesis from Fürstner’s group was the first synthesis showing Grubbs RCM could be applied to zearalenone, as well as the first zearalenone synthesis utilizing kinetic resolution of a racemic starting material for the installation of absolute stereochemistry.

1.2.9 Biomimetic Syntheses

In 2008, Barrett published a biomimetic synthesis of (S)-zearalenone,31 featuring a late-stage aromatization on Dowex resin. The synthesis started from racemic δ-hexanolide (22.1), which was ring-opened by a 4-pentenyl Grignard addition to form 22.2. The resulting alcohol 22.2 was protected with acetic anhydride to give acetate 22.3, and the ketone was protected to give ethylene ketal 22.4. Deprotection of the racemic alcohol was followed by an enzyme-mediated kinetic resolution with CAL-B lipase and vinyl acetate to give the optically pure alcohol (S)-22.5. The synthesis of the aromatic fragment began with an aldol reaction between (E)-crotonaldehyde (22.6) and ethyl acetate (22.7).32 The resulting alcohol 22.8 was protected as TBS ether 22.9, and the ester was reduced to the corresponding aldehyde 22.10 with DIBAL-H. The last fragment was the TBS enolate of commercially available 22.11.

Fragments 22.12 and 22.10 were coupled by a Mukaiyama aldol reaction with boron trifluoride diethyl etherate, and the resulting alcohol 22.13 was oxidized to ketone 22.14 by a Dess-Martin oxidation. The TBS group was deprotected, and also oxidized by Dess-Martin periodinane to give 22.15. Dione 22.15 was coupled with the optically pure fragment (S)-22.5 in toluene at reflux to afford 22.16. Sequential treatment with potassium methoxide and Dowex
resin 50WX8-400 achieved the desired biomimetic aromatization giving resorcylic acid derivative 22.17. The macrocycle was closed by a Grubbs RCM with the 2\textsuperscript{nd} generation Grubbs-Hoveyda catalyst 22.18 to afford the product, 22.19, in an excellent yield of 68\% over the last 4 steps. With this biomimetic approach, no final deprotection of the phenols was necessary, a great advantage considering the low yields reported previously for said deprotection.

**Scheme 22. Biomimetic synthesis from Barrett’s group in 2008.**
Barrett published again in 2010\textsuperscript{33} an improved synthesis of (S)-zearalenone which featured the same late-stage aromatization, but used a different macrolactonization. The synthesis started from 5-norbornene-2-carboxylic acid (23.1), which was coupled with ethyl acetate using CDI. The product, β-ketoester 23.2, was protected as an ethylene ketal, and the norbornene ring was removed by flash vacuum pyrolysis. Ethyl ester 23.4 was hydrolyzed with potassium hydroxide, and the acid intermediate was converted into 1\textit{H}-benzotriazole 23.5. The amide 23.5 was then coupled with the lithium enolate of 23.6 in the presence of zinc(II) chloride to give 22.7. The chiral fragment 23.8 (22.5 in Scheme 22) was cross-coupled to 23.7 by a Grubbs metathesis with the 2nd generation Grubbs catalyst 23.8. To cyclize the resulting olefin
Barrett used a macrocyclic ketene-trapping approach. This was accomplished by refluxing 23.9 in toluene forming a ketene intermediate 23.10 which reacted to form 23.11. The two protected ketones were deprotected with p-TsOH, and the late-stage aromatization was achieved again by sequential treatment of 23.12 with cesium carbonate in methanol, acetic acid, and hydrogen chloride. This successfully gave the product 23.13 in an overall yield of 7.4%, similar to previously achieved yields.

1.2.10 Novel Route Utilizing Diels-Alder Chemistry

In 2011, Yadav’s group took an interesting approach to the aromatic portion of (S)-zearalenone. First, propargylic ester 24.3 was prepared by TBS protection of 24.1 and coupling with methyl chloroformate in the presence of n-butyllithium to form 24.3. Aromatization was then achieved by a Diels-Alder/retro-Diels-Alder reaction between commercially available cyclic diene 24.4 and alkyne 24.3. The product, resorcylic acid derivative 24.5, was treated with hydrofluoric acid in pyridine to deprotect the TBS ether. The alcohol 24.6 was converted to iodide 24.7 by iodine in triphenylphosphine. Elimination of the iodide afforded benzylic olefin 24.8, which was saponified by lithium hydroxide in water to give free acid 24.9 in 19.9% yield from 3-butyn-1-ol.
The chiral fragment of the molecule was synthesized from 5-hexen-1-ol (24.10) by first protecting the alcohol as THP ether 24.11. Epoxidation with m-CPBA gave racemic epoxide 24.12, which was asymmetrically resolved with Jacobsen catalyst 24.13 in acetic acid to achieve optically pure 24.12. Reductive opening of the epoxide 24.12 gave alcohol 24.14, which was
promptly protected as TBDPS ether 24.15. The THP group was removed with PPTS, and the alcohol was oxidized with IBX in DMSO to the corresponding aldehyde 24.16. The aldehyde was subjected to a Grignard reaction to add the 4-pentenyl group and the alcohol 24.17. The alcohol was protected as a THP ether, and the TBDPS group was removed to give 24.18. This fragment was then coupled with aromatic fragment 24.9 by a Mitsunobu reaction to give ester 24.19. The THP group was deprotected to form 24.20, which was then cyclized via a Grubbs RCM to form 24.22. The newly formed macrolactone 24.22 was oxidized with IBX and deprotected with aluminum iodide and TBAI to give (S)-zearalenone (24.23) in 1.3% overall yield from 3-butyn-1-ol. The novel Diels-Alder approach unfortunately suffered from a low yield, and the use of kinetic resolution also hurt the overall yield.

1.2.11 First Use of Non-Enzymatic Asymmetric Catalysis

Feringa’s and Minnaard’s groups published the first asymmetric synthesis of (S)-zearalenone that did not use an enzyme, resolution, or optically pure starting material in 2013.35 First, 1-bromo-3,5-dimethoxybenzene was formylated by a Vilsmeier-Haack reaction to produce aldehyde 25.2. Stille coupling added a vinyl group at the bromide’s position to give benzylic olefin 25.3. The aldehyde was then converted to acid 25.4 by a Pinnick oxidation, then to fluoride 25.5 by the addition of cyanuric fluoride in pyridine.
Another building block was synthesized from acetyl chloride (25.6), first by cuprate addition of the 4-pentenyl group, then by subsequent conversion of ketone 25.7 into dimethyl hydrazone 25.8. The last fragment was built from acrolein (25.9), first by zinc(II) chloride-catalyzed benzoylation and rearrangement to 25.11 via 25.10. A copper-mediated methylmagnesium bromide addition enantiospecifically gave 25.12 with a catalytic amount of CuBr-DMS and chiral ligand Taniaphos. The reaction furnished α-methyl benzoate 25.12 in 82% yield with 98% enantiomeric excess. It is worth noting that this was the first application of non-enzymatic asymmetric catalysis to zearalenone synthesis, a significant feat as it did not require
stoichiometric amounts of expensive chiral auxiliaries or starting materials, nor did it suffer from reduced yield by kinetic resolution. The benzoate was removed with KOH and replaced with a TBDPS ether (25.13). Hydroboration-oxidation added a hydroxyl group in anti-Markovnikov fashion, and the alcohol 25.14 was converted into iodide 25.15. The iodide was coupled with the lithium anion of hydrazone building block 25.8 to afford ketone 25.16. The ketone was protected as an ethylene ketal, and the TBDPS ether was removed to give alcohol 25.17. The alcohol was combined with aromatic fragment 25.5 with KHMDS to form RCM precursor 25.18. The ring closure was achieved by use of the Grubbs II RCM catalyst 25.19. The closed macrolactone 25.20 was finally deprotected to give ((S))-zearalenone (25.21) in 7.8% overall yield from acrolein.

1.2.12 Yadav’s Improved Synthesis

Yadav’s group published a 2nd synthesis of ((S))-zearalenone in 2016\textsuperscript{36} with a major improvement in yield, though it utilized an expensive chiral reagent, ((S))-4-penten-2-ol (which can be made from ((S))-propylene oxide). The synthesis began from 2,4,6-trihydroxybenzoic acid, which was protected as acetonide 26.2. The \textit{para} phenol was protected as a methyl ether, and the \textit{ortho} phenol was converted into triflate 26.3. A Stille coupling was utilized to replace the triflate with a vinyl group, yielding 26.4. The best conditions for the Stille coupling were found to be the use of palladium catalyst tris(dibenzylideneacetone)dipalladium(0), NMP, and additives lithium chloride and tri(2-furyl)phosphine (TFP) at 60 °C (88% yield). The resulting alcohol was subjected to TEMPO/BAIB oxidation to afford aldehyde 26.5. The aldehyde was reacted with vinylmagnesium bromide, and the mixture of diastereomeric alcohols was protected to give TBS ethers 26.6. Chiral reagent ((S))-4-penten-2-ol was added as a sodium alkoxide to the ester 26.6 to give ester 26.7. The TBS-protected alcohol was then deprotected and oxidized by Dess-Martin
periodinane. Ring-closing metathesis of 26.8 with 2nd generation Grubbs catalyst 26.9 proceeded in 75% yield, and the newly formed olefin was selectively reduced by copper(I) hydride, formed \textit{in situ} by copper(I) bromide and Red-Al. Final deprotection of the phenol gave the product, 26.10, in an extraordinarily high overall yield of 19.1%.

\textbf{Scheme 26. Yadav’s 2016 synthesis with improved yield.}

1.3 \textbf{Summary}

Zearalenone has served as a great test case for the development of synthetic methods. Though there have been over 20 publications on the synthesis of zearalenone, only one of them utilized a non-enzymatic asymmetric catalysis that did not involve a resolution, and only one achieved a high yield (>10%). Massive improvements were made since Wendler’s and Cross’s
original 1967/1968 syntheses, which suffered from abysmally low yields. Significantly, Wendler did successfully determine the absolute configuration of naturally occurring (−)-zearalenone. The development of Corey-Nicolaou and Masamune macrolactonizations was a significant achievement in terms of yield improvement. Tsuji’s group made several more contributions diversifying the synthetic routes, including their uses of intramolecular alkylation and protected cyanohydrins. Enantiopure zearalenone was not synthesized until 1990, when Pattenden and Hitchcock derived the chiral center from naturally occurring parasorbic acid. In addition, they presented a new radical macrocyclization method. The first true asymmetric synthesis occurred the following year by Keinan’s group, utilizing an enzyme-catalyzed reduction. The same year, Hegedus’s group achieved the first application of the Stille coupling to enantiopure zearalenone synthesis, deriving their chiral purity from (R)-propylene oxide. Nicolaou’s group again applied the Stille coupling to zearalenone synthesis, reporting a solid-phase synthesis on Merrifield resin.

In 2000, Fürstner introduced the application of Grubbs RCM to zearalenone synthesis, which continued to be used for all future syntheses. Barrett’s biomimetic syntheses in 2008 and 2010 showed the utility of late-stage aromatization for preparing zearalenone from non-aromatic starting materials, while Yadav’s 2011 synthesis presented an alternative Diels-Alder/retro-Diels-Alder-oriented approach to the aromatic fragment. Feringa’s and Minnaard’s groups synthesized (S)-zearalenone in 2013 via asymmetric catalysis, a significant improvement in cost-efficiency. Finally, the recent 2016 synthesis by Yadav greatly improved upon yield but required an expensive chiral starting material. Despite all of these improvements, there still has not been a zearalenone synthesis published that achieved an asymmetric synthesis via catalysis in high overall yield rather than chiral starting materials (or auxiliaries) or kinetic resolution.
Chapter 2: New Synthetic Strategy Towards Zearalenone

2.1 Retrosynthetic Analysis of Zearalenone

Given the lack of a truly practical asymmetric synthesis of zearalenone, the development of a practical *de novo* asymmetric approach is an apt target for this thesis. Additionally, the enantiomer of zearalenone has not yet been synthesized in optically pure form, so a route to *ent*-zearalenone is desirable as a potentially nontoxic control molecule. The advantage of an asymmetric synthesis where the absolute stereochemistry is controlled by catalyst is that both enantiomers are equally available. For our synthesis, we decided to do the ring closure via a Grubbs’ ring-closing metathesis, since there is precedent for consistently high yields and the disconnection does not affect stereochemistry at the chiral center. Additionally, the molecule is initially synthesized with the olefin one position further from the aromatic ring, avoiding any potential issues with reactivity that could result from benzylic stabilization. The olefin can easily be isomerized to be in conjugation with the aromatic ring at the end of the synthesis by treatment with DBU.

The lactone is envisioned to be constructed under Steglich conditions, using DCC. The acid fragment 27.3 can be synthesized from commercially available 2,4,6-trihydroxybenzoic acid monohydrate either by the known Stille coupling or by a novel Suzuki coupling with allyl pinacol boronate. The chiral fragment 27.4 can be synthesized from terminal alkyne 27.9 via a gold-catalyzed hydroalkoxylation and Claisen rearrangement. The racemate of the terminal alkyne can be prepared from commercially available 5-hexyn-1-ol via a known Parikh-Doering oxidation of the alcohol followed by a Grignard addition of the methyl group. On the other hand, the enantiopure (R)-27.9 can be synthesized by a *de novo* asymmetric approach that uses a
Noyori/zipper strategy. This diverse strategy has been used to synthesize several natural products from exclusively cheap, achiral molecules.

Scheme 27. Retrosynthesis for the present synthesis of zearalenone.

2.2 The De Novo Asymmetric Noyori-Zipper Paradigm

The synthesis of enantiopure (R)-(+) - zearalenone starts with the “Noyori-Zipper paradigm”, a reaction sequence which has been used by the O’Doherty group to synthesize several other macrolactone natural products in de novo asymmetric fashion, including cladospolide B, phoracantholide J, tetrahydrolipstatin, and the disaccharide macrolactone fragment of batatinoside III (Scheme 28). The Noyori-zipper reaction sequence can easily provide building blocks for macrolactones of varying sizes, simply by varying the number of carbons in the aldehyde and/or alkyne starting material. Xing and O’Doherty’s 2009 synthesis of
cladospolides B-D utilized this approach to assemble the key carbon fragments from 1-nonyne and acetaldehyde.\textsuperscript{37} Similarly, Sharif \textit{et al}.’s 2014 synthesis of merremoside D used 1-undecyne and caproaldehyde,\textsuperscript{38} and Avocetien \textit{et al}.’s 2016 synthesis of phoracantholide J used 1-pentyne and acetaldehyde as starting materials.\textsuperscript{39} In this thesis, the use of the Noyori-zipper sequence to synthesize \textit{ent}-zearalenone is reported. The sequence starts by Noyori reduction of an \(\alpha,\beta\)-ynone to a propargyl alcohol, which can then be isomerized to a terminal alkynol without loss of optical purity.

\textbf{Scheme 28. Applications of the Noyori-Zipper reaction sequence.}

\begin{center}
\includegraphics[width=\textwidth]{scheme28.png}
\end{center}

2.3 \textbf{Noyori Asymmetric Hydrogenation}

In this approach, enantiopurity is introduced via the Noyori asymmetric hydrogenation, which utilizes a chiral ruthenium catalyst (\textbf{Fig. 2}) to convert an aryl or alkynyl ketone to an optically enriched chiral alcohol with yields as high as 90-95\% and enantiomeric excess as high as 99.5\%. The original catalysts developed by Ryoji Noyori \textit{et al}. in 1987\textsuperscript{40} are ruthenium dihalides with the chiral BINAP ligand, in addition to a diamine ligand for non-functionalized
ketones. However, in 1995 Noyori’s group published additional papers\textsuperscript{41,42} investigating how to achieve similar yields and stereoselectivities with a wider array of substrates and higher catalytic efficiency. This alternative method has the advantage of using formic acid in place of hydrogen gas, and is more compatible with alkene and alkyne substrates. It was found that by utilizing DPEN-based ruthenium(II) catalysts, substrate/catalyst (S/C) mole ratios as high as 5000 could be used while maintaining excellent yields and stereoselectivities. Catalysts containing TsDPEN and mesitylene in place of BINAP and one chloride worked best for aromatic ketones. This variant of the Noyori catalyst is predominantly used in the O’Doherty lab’s syntheses. The catalysts still give exceptionally high yields and enantiomeric excess when utilizing formic acid as a hydrogen source,\textsuperscript{43} providing a consistent and clean method for introducing chirality into a molecule without the need for hydrogen gas at high pressures.

![Catalysts for Noyori asymmetric hydrogenation](image)

**Figure 2.** Catalysts for Noyori asymmetric hydrogenation.

### 2.4 Alkyne Zipper Reaction

After introducing chirality via the Noyori reaction, the alkyne zipper reaction is utilized to convert the internal alkyne to a terminal alkyne. The superbase reagent KAPA, potassium 3-aminopropylamide, is generated *in situ* from potassium hydride and 1,3-diaminopropane. This reaction affords an ω-ynol building block containing both a hydroxyl group and a terminal alkyne with no loss of enantiomeric excess. The alkyne zipper reaction occurs via a deprotonation/protonation mechanism (Scheme 29) with allene and alkyne intermediates. As the π-bonds isomerize towards the end of the carbon chain, the reaction effectively becomes
irreversible due to the significantly lower $pK_a$ of the final acetylenic proton compared to those of the intermediate propargylic and allenic protons.$^{44}$ The reaction can then be quenched with water to yield the terminal alkyne product 29.11. The alkyne zipper reaction originally was performed using potassium amide or potassium hydroxide, and under these conditions required high temperature and long reaction times. These reaction conditions also led to a mixture of isomers in the product (including allene and internal alkyne intermediates) and polymerization of the alkyne. The discovery of the KAPA reagent in 1974 by Charlie Brown$^{45,46}$ completely changed the practicality of the zipper reaction, as the reaction can be completed in only a few minutes at room temperature when KAPA is utilized. KAPA provides faster reactivity due to its amphoteric properties – deprotonation/protonation is rapid as both the amine and amide moieties are present at any given time. The zipper reaction also works on a wider variety of substrates when KAPA is used, including isomerization of benzylic alkynes as shown in Scheme 29. The reaction was further popularized in 1988 when Abrams published on a modification of the zipper reaction using potassium t-butoxide and lithium, as these reagents were easier to handle. However, the potassium hydride and 1,3-diaminopropane protocol was used in this synthesis of zearalenone as it consistently offered more satisfactory results.
2.5 Gold-Catalyzed Hydroalkoxylation

Following the Noyori-zipper reaction sequence, the next key reaction in this synthesis is a gold-catalyzed hydroalkoxylation of a terminal alkyne. The gold(I)-catalyzed hydroalkoxylation of a terminal alkyne was first reported by Teles in *Angew. Chem. Int. Ed.* 1998. Teles posited that the reaction mechanism started from gold-coordinated alkyne 30.2, proceeding via cyclic intermediate 30.5 after addition of the alcohol 30.3. Teles’s proposed mechanism then indicated the 5-membered ring collapsing into a 3-membered ring 30.6 before releasing the product, 30.7. By 2014, the generally understood mechanism was that shown in Scheme 31. The mechanism has four key steps, the first of which is alkyne substrate 31.2 being complexed with cationic gold(I) catalyst 31.1. The newly formed complex 31.3 activates the alkyne for nucleophilic attack by alcohol 31.4 to form a vinyl gold complex 31.6 via the protonated vinyl ether 31.5. Fürstner showed in 2010 that the complex 31.6 is aurophilic, and equilibrates with a gem-diaurated derivative 31.7 by the addition of another equivalent of the gold catalyst. Protonation then releases the product 31.8 and starts the catalytic cycle once more.
Scheme 30. First proposed mechanism for gold(I)-catalyzed hydroalkoxylation.

Scheme 31. Overview of corrected hydroalkoxylation catalytic cycle.

Zhdanko published a series of detailed mechanistic studies on the gold(I)-catalyzed hydroalkoxylation of alkynes in 2014-15. In them, he described a more detailed mechanism for this reaction (Scheme 32). Specifically, he identified which steps are irreversible and which steps are reversible. Zhdanko identified the formation of diaurate 32.7 (31.7) as a potential hindrance to the catalytic cycle, as it traps gold species in a highly thermodynamically favorable manner. The key takeaway from his first mechanistic study was that the formation of 32.7 needs to be accounted for and counteracted. This is possible by using bulkier ligands, more branched substrates, and acid promoters.
For this synthesis of zearalenone, the bulky ligand triphenylphosphine has been used with moderate success, and future plans include also testing the much bulkier, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene ligand. Zhdanko’s group also studied the effect of silver additives on gold(I)-catalyzed hydroalkoxylation, and found that the effects can be positive, negative, or nonexistent depending on the substrate. In the reaction between 3-hexyne and deuterated methanol, the silver ions were found to have no effect on disappearance of the starting material. Thus, a silver additive could likely be used for the hydroalkoxylation of the Noyori-zipper product without inhibiting the catalytic cycle.

**Scheme 32. Detailed mechanism of gold(I)-catalyzed hydroalkoxylation.**

2.6 **Claisen Rearrangement**

The Claisen rearrangement, first reported on in *Ber. dtsch. chem. Ges.* 1912, was the first recorded example of a [3,3]-sigmatropic rearrangement, and has since been used extensively as a powerful carbon-carbon bond-forming tool. The rearrangement is best applied to allyl vinyl ethers, and requires only heat to proceed. The product of the rearrangement is a γ,δ-unsaturated ketone. The reaction is a concerted, pericyclic reaction, and is suprafacial as predicted by the
Woodward-Hoffmann rules. When the reaction, shown in Scheme 33, occurs via a single chair-like transition state, it is highly stereoselective.

**Scheme 33. Mechanism of the stereospecific Claisen rearrangement.**

In *Chem. Commun.* 2013, Aponick et al. reported that an intermolecular hydroalkoxylation with an allylic alcohol and subsequent Claisen rearrangement could be carried out in tandem from alkynes. This strategy can efficiently provide allyl vinyl ethers for the Claisen rearrangement, while also undergoing the rearrangement in one pot. The most common conditions are 5 mol% isopropylgold(I) chloride and silver tetrafluoroborate in THF, from 65 °C to 120 °C. Under these conditions for various substrates, yields (50% to 99%), but diastereomeric ratios varied (3:1 to >25:1); better diastereoselectivity was achieved when sterically bulky or polar substituents were used. Use of relatively small, nonpolar groups such as ethyl and even n-hexyl showed very little diastereoselectivity. Regioselectivity when asymmetric internal alkynes were used was dependent on the electron-donating or electron-withdrawing effects of the substituents, with α-aryl ketones being favored in an electron-deficient environment and β-aryl ketones being favored in an electron-rich environment. However, Aponick’s group did not test any non-aryl asymmetric alkynes, nor did they test any terminal alkynes.
Scheme 34. Aponick's optimized hydroalkoxylation/rearrangement conditions.

The following year in *ACS Catal.*, Nolan *et al.* investigated further into this tandem hydroalkoxylation/rearrangement, seeking to develop a more “green” approach. Using Aponick’s work as a basis, they sought to remove the necessity of additives for activating the catalyst, reduce their environmental impact, improve TON (turnover number) and TOF (turnover frequency), and increase mass efficiency.\(^{53}\) The optimal conditions for these goals were 0.2 mol% of the \([1,3\text{-bis}(2,6\text{-diisopropylphenyl})\text{imidazol-2-ylidene}][\text{bis(triflyl)}\text{imide}]\text{gold(I)}\) catalyst, 3 equivalents of the allylic alcohol, and 120 °C. The reactions were conducted using the allylic alcohol itself as the solvent, also reducing environmental impact. For aryl terminal alkynes, yields ranged from 48-77%, and complete regioselectivity was observed. The new methodology gave TONs of 96-465 (compared to Aponick’s 10-20) and TOFs of 6-1396 h\(^{-1}\) (compared to Aponick’s 0.5-1 h\(^{-1}\)). However, the tandem gold(I)-catalyzed hydroalkoxylation and Claisen rearrangement of an aliphatic terminal alkyne has still not been reported until this thesis.

Scheme 35. Nolan's optimized hydroalkoxylation/rearrangement conditions.
2.7 Summary

This synthesis route to zearalenone features a variety of intriguing reactions, and is expected to yield an optically enriched product in high yield without the use of chiral auxiliaries, chiral resolution, enzymes, or enantiopure starting materials. The aliphatic fragment of the (\(R\))-enantiomer of zearalenone can be synthesized by use of a previously applied Noyori-zipper reaction sequence, a method which has produced other optically enriched compounds in high yield. The Noyori asymmetric hydrogenation is among some of the most stereoselective reactions currently developed, and is expected to proceed with over 95% enantiomeric excess to yield a propargyl alcohol. Furthermore, the alkyne zipper reaction as performed with potassium hydride and 1,3-diaminopropane is capable of isomerizing internal alkynes such as this propargyl alcohol to terminal alkynes without loss of optical purity. A tandem gold(I)-catalyzed hydroalkoxylation and Claisen rearrangement will then be thoroughly investigated to find optimal conditions leading directly to the protected aliphatic fragment of (\(R\))-zearalenone. The hydroalkoxylation is a relatively novel reaction shown to regioselectively add allylic alcohols to terminal alkynes, and in addition the gold catalysts used for this reaction are believed to facilitate a following Claisen rearrangement, providing the desired fragment.
Chapter 3:

Synthesis of Racemic and Enantiopure Samples of Zearalenone

3.1 Synthesis of the Aliphatic Fragment of (R)-(+) Zearalenone

This asymmetric synthesis of zearalenone starts from the inexpensive, achiral, commercially available compounds acetaldehyde (36.1) and 1-pentyne (36.2). The two starting materials were coupled by an n-BuLi-mediated alkyne metalation and aldehyde addition to give propargyl alcohol (±)-36.3 as a mixture of enantiomers in 90% yield. Next, the racemic alcohol was oxidized to ynone 36.4 with manganese dioxide in 90% yield. The ynone 36.4 was then reduced via a Noyori asymmetric hydrogenation with the (R,R)-Noyori catalyst and CTAB. Formic acid was used as a hydrogen source, and the reaction gave optically enriched (R)-36.3 in 95% yield. This material was subjected to an alkyne zipper reaction with KAPA, formed in situ from potassium hydride and 1,3-diaminopropane. The zipper reaction provided terminal alkyne 36.5 in 85% yield. Protection of the alcohol with benzoyl chloride afforded benzoate 36.6 in 84% crude yield, but purification is still in progress. For the gold(I)-catalyzed hydroalkoxylation and Claisen rearrangement, the conditions to form ketone 36.8 are currently being optimized. The next step will be deprotection of the benzoate group to alcohol 36.9.

Scheme 36. Noyori-zipper approach to (R)-36.9.

![Scheme 36. Noyori-zipper approach to (R)-36.9.](image-url)
3.2 Synthesis of the Racemic Variant of the Aliphatic Fragment of Zearalenone

To synthesize the racemic variant of aliphatic fragment 36.9, a shorter route was easily developed as there was no need for stereoselectivity. The route started from ω-hydroxy terminal alkyne 5-hexyn-1-ol (37.1). A Parikh-Doering oxidation was used to oxidize the alcohol to aldehyde 37.2 in 93% yield. Next, a Grignard addition of methylmagnesium bromide afforded alcohol (±)-37.3 – the racemic variant of 36.5 – in 74% yield. Protection of the alcohol as a benzoate group gave (±)-37.4 in 84% crude yield, but purification is still in progress. Optimal conditions for the tandem gold(I)-catalyzed hydroalkoxylation and Claisen rearrangement are currently being investigated, to obtain ketone (±)-37.6. As in the Noyori-zipper route, the next step will be deprotection of the benzoate group with potassium carbonate.

Scheme 37. Short route to racemic fragment 37.7.

![Scheme 37](image)

3.3 Synthesis of the Resorcylic Acid Fragment of Zearalenone

Turning to the synthesis of the resorcylic acid fragment, starting material 2,4,6-trihydroxybenzoic acid monohydrate (38.1) was protected as acetonide 38.2 in 77% yield using trifluoroacetic acid and trifluoroacetic anhydride in acetone. The phenols of 38.2 were then protected as methyl esters with methyl iodide, giving 38.3 in 81% yield. Acetonide 38.3 was opened by treatment with potassium carbonate in methanol to give methyl ester 38.4, and the phenol of 38.4 was converted to triflate 38.5 by treatment with triflic anhydride and pyridine in 81% yield over both steps. Purification of the triflate is still in progress. The next step, which is
under current investigation, will be a palladium-catalyzed cross-coupling to couple an allyl group to the triflate 38.5. Two methods are being investigated; the first is a Suzuki coupling between allyl pinacol boronate and the triflate, catalyzed by tris(dibenzylideneacetone)palladium(0) with additive CsF. This coupling has not yet been reported. The alternative is a Stille coupling between tri-\textit{n}-butylallylstannane and the triflate, using the same palladium catalyst but with LiCl and tri(2-furyl)phosphine (TFP) as additives. Either coupling is expected to provide 38.6 in good yield. The methyl ester can then be deprotected by treatment with lithium hydroxide to afford carboxylic acid 38.7.

**Scheme 38. Synthesis of the aromatic fragment of zearalenone.**

3.4 **Completion of the Total Synthesis of Zearalenone**

This total synthesis of zearalenone is not yet complete as a result of time constraints; however, shown in **Scheme 39** is the planned route from fragments 39.1 and 39.2a/b to \textit{ent-} and \textit{rac-} zearalenone respectively. The two fragments will be coupled with DCC in a Steglich esterification to afford the ester 39.3a or 39.3b. Next, the 2\textsuperscript{nd} generation Grubbs catalyst will be used for RCM to give the olefin 39.4a or 39.4b. Isomerization of the olefin with DBU will afford
dimethylzearalenone (39.5a/b), and removal of the methyl ethers will give the final product, (R)-(+)-zearalenone (39.6a) or (±)-zearalenone (39.6b).

Scheme 39. Completion of total synthesis of zearalenone.

3.5 Future Plans

In addition to completing the total syntheses of both (R)-zearalenone and racemic zearalenone, further related studies are planned. Zearalenone will be tested in biological assays to evaluate its activity and potential medicinal applications. Additionally, other resorcylic acid lactones such as zeranol and zearalanone may be synthesized from zearamelone or via independent routes. Zearalenone also has two free phenol groups that could be glycosylated, and these zearalenone glycoside derivatives may reveal additional activity of the natural product. The phenol groups of naturally occurring zearalenone are often glycosylated, suggesting these products have medicinal relevance.4,5,54

3.6 Summary of Zearalenone Synthetic Efforts

A novel de novo asymmetric synthesis of model compound zearalenone has been initiated with promising early results, though the synthesis is incomplete due to time constraints. The Noyori-zipper sequence proceeded in high yield without loss of optical purity, while the hydroalkoxylation and Claisen rearrangement are currently being optimized along with the
palladium-catalyzed cross-coupling of the resorcylic acid fragment. If the remainder of the route proceeds as smoothly as expected, this synthesis will be the first high-yield *de novo* asymmetric synthesis of zearalenone, using only non-enzymatic asymmetric catalysis to achieve optical purity.
4.1 General Information

$^1$H and $^{13}$C NMR spectra were recorded on a Varian 400, 500 or 600 MHz spectrometer. Chemical shifts were reported relative to CDCl$_3$ ($\delta$ 7.26 ppm) for $^1$H NMR and CDCl$_3$ ($\delta$ 77.2 ppm) for $^{13}$C NMR. Infrared (IR) spectra were obtained on a FT-IR spectrometer. Optical rotations were measured with a digital polarimeter in the solvent specified. Flash column chromatography was performed on 60-200 or 230-400 mesh silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates and visualized by quenching of fluorescence and by charring after treatment with $p$-anisaldehyde or potassium permanganate stain. $R_f$ values were obtained by elution in the stated solvent ratios. Tetrahydrofuran (THF), methylene dichloride (CH$_2$Cl$_2$) and dimethylformamide (DMF) were dried by passing through activated alumina column with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven- or flame-dried glassware and standard syringe/septa techniques.

4.2 Experimental Procedures

$\text{(+/-)-hept-3-yn-2-ol ((\pm)-36.3):}$

\[ \text{MeCHO} + \text{MeCHCH\text{}}_3 \xrightarrow{\text{n-BuLi, THF, -78 °C}} \text{MeCHCH\text{}}_3\text{O} \]

To a stirred solution of 1-pentyne (1.50 g, 22.1 mmol) in dry THF (44 mL) at $-78 \, ^\circ\text{C}$ under argon was added a solution of $n$-BuLi in hexane (11.1 mL, 26.5 mmol) dropwise. After 30 min, acetaldehyde (1.20 mL, 22.1 mmol) was added. The reaction was warmed to 0 °C and stirred for

65
10 min and then warmed to RT for 50 min. Additional CH₂Cl₂ (10 mL) was added to the reaction mixture followed by saturated aqueous NH₄Cl (20 mL). The aqueous phase was separated and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated. Chromatography on silica gel gave (+/-)-hept-3-yn-2-ol (±)-36.3 (2.23 g, 19.9 mmol, 90%) as a colorless oil: Rf = 0.28 (10% EtOAc/hexane); IR (neat): 3340, 2958, 2869, 2244, 1458, 1291, 1155, 1074, 893 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 4.45 (qt, J = 6.6, 1.8 Hz, 1H), 2.10 (td, J = 6.6, 1.8 Hz, 2H), 1.45 (qt, J = 7.2, 6.6 Hz, 2H), 1.35 (d, J = 6.6 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H) ppm; ¹³C NMR (150 MHz, CDCl₃) δ 84.1, 82.4, 58.2, 24.5, 21.9, 20.5, 13.2 ppm.

**hept-3-yn-2-one (36.4):**

\[ \text{Me}_3\text{C}=-\text{O} \]

To a solution of (±)-36.3 (4.00 g, 35.7 mmol) in THF (100 mL) at room temperature was added activated MnO₂ (20.0 g, 0.23 mol). The reaction mixture was stirred for 24 h then filtered through Celite and concentrated under pressure to give hept-3-yn-2-one 36.4 (3.53 g, 32.12 mmol, 90%) as a yellow oil. Rf = 0.40 (10% EtOAc/hexane); IR (neat): 2960, 2871, 2210, 1675, 1358, 1226 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 2.30 (t, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.57 (qt, J = 7.2, 7.2 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H) ppm; ¹³C NMR (150 MHz, CDCl₃) δ 184.8, 93.8, 81.4, 32.6, 21.1, 20.7, 13.3 ppm.

**((R))-hept-3-yn-2-ol ((R)-36.3):**

\[ \text{Me}_3\text{C}=-\text{O} \]

(R)-hept-3-yn-2-ol ((R)-36.3):
To a flask was added ketone 36.4 (10.8 g, 86.9 mmol), 2 M sodium formate in water (400 mL) and cetyl trimethylammonium bromide (3.17 g, 8.69 mmol). The mixture was stirred at room temperature for 5 min, and then (R,R)-Noyori catalyst (105 mg, 0.174 mmol) was added. The reaction mixture was stirred for 24 h. The reaction was then diluted with water and extracted with Et₂O, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give alcohol (R)-36.3 (9.30 g, 83.05 mmol, 95%) as a colorless oil: \( R_f = 0.28 \) (10% EtOAc/hexane); \([\alpha]_D^{25} = -10.3\) (c = 0.29, MeOH); IR (neat): 3340, 2958, 2869, 2244, 1458, 1291, 1155, 1074, 893 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl₃) \( \delta 4.45 \) (qt, \( J = 6.6, 1.8 \) Hz, 1H), 2.10 (td, \( J = 6.6, 1.8 \) Hz, 2H), 1.45 (qt, \( J = 7.2, 6.6 \) Hz, 2H), 1.35 (d, \( J = 6.6 \) Hz, 3H), 0.91 (t, \( J = 7.2 \) Hz, 3H) ppm; \(^13\)C NMR (150 MHz, CDCl₃) \( \delta 84.1, 82.4, 58.2, 24.5, 21.9, 20.5, 13.2 \) ppm.

(R)-hept-6-yn-2-ol (36.5):

A 30% suspension of KH in mineral oil (5.62 g, 140 mmol) was washed three times under argon with ether, and then the excess solvent was removed under vacuum. Dry 1,3-diaminopropane (28 mL) was added at 0 °C. The reaction was warmed slowly to room temperature with stirring over 1 h. Then the mixture was cooled to 0 °C, and the alkynol (R)-36.3 (3.15 g, 28.1 mmol) was added dropwise over 20 min. The resulting slurry was warmed to room temperature and stirred at the same temperature. The completion of reaction was monitored by TLC. The mixture was cooled to 0 °C, and ice chips were added slowly and extracted with ether. The combined extracts were washed with 1 N HCl, saturated aqueous sodium bicarbonate and brine, and then dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was purified by flash
chromatography (Et₂O/hexane 20-30%) to give **36.5** (2.71 g, 24.2 mmol, 85%) as a colorless oil. 

R_f = 0.28 (20% EtOAc/hexane): [α]_D²⁵ = +8.0 (c = 1.0, CHCl₃); IR (neat): 3309, 2934, 2862, 2117, 1460, 1432, 1374, 1128, 1093, 937, 821 cm⁻¹; ^1H NMR (600 MHz, CDCl₃) δ 3.83 (qt, J = 6.0, 6.0 Hz, 1H), 2.23 (td, J = 7.2, 3.0 Hz, 2H), 1.95 (t, J = 3.0 Hz, 1H), 1.67—1.56 (m, 4H), 1.20 (d, J = 6.0 Hz, 3H) ppm; ^13C NMR (150 MHz, CDCl₃) δ 84.3, 68.5, 67.6, 38.2, 24.7, 23.6, 18.4 ppm.

(+/−)-hept-6-yn-2-ol ((±)-37.3):

To a flask was added 2.3 mL of **37.1**, followed by 15 mL of extra-dry DMSO. The solution was stirred at RT. To the reaction flask was then added 14.20 mL of Et₃N. The reaction was cooled to 0 °C, and to it was added 8.10 g of sulfur trioxide-pyridine complex. The reaction was slowly warmed to RT and continued stirring for 18 hours. Nitrogen gas was bubbled through the reaction mixture into bleach to remove and neutralize DMS gas. The reaction was then quenched with 25% EtOAc/hexanes and extracted from water. The product was extracted twice more with 25% EA/hexanes, then washed sequentially with sodium bisulfate, sodium bicarbonate, and brine. The recovered organic layer was dried over sodium sulfate, yielding 1.8 g of a yellow oil (93%). The product was used without further purification.

To a chilled flask was added 8.5 mL MeMgBr, 3.0 M in Et₂O, followed by 15 mL of anhydrous Et₂O. To the reaction flask was then added 1.8 g of **37.2**. The solution was stirred at 0 °C for 16 hours, then quenched with Et₂O and aqueous sodium bisulfate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 5-50%) and concentrated by rotary
evaporation to give 1.70 g of (±)-37.3 (74%). R<sub>f</sub> = 0.28 (20% EtOAc/hexane); IR (neat): 3309, 2934, 2862, 2117, 1460, 1432, 1374, 1128, 1093, 937, 821 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.81 (m, 1H), 2.20 (m, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.68-1.51 (m, 5H), 1.18 (d, J = 6.2 Hz, 3H) ppm; <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 84.35, 68.50, 67.57, 38.16, 24.65, 23.55, 18.34 ppm.

**(R/S)-hept-6-yn-2-yl benzoate ((±)-37.4):**<sup>55</sup>

![Chemical Structure](https://example.com/structure.png)

To a flask was added 200 mg of (±)-37.3 and 9 mL of CH<sub>2</sub>Cl<sub>2</sub> with stirring at RT. To this solution was then added, sequentially, 447 µL of Et<sub>3</sub>N, 290 µL of benzoyl chloride, and 109 mg of DMAP. The reaction continued stirring at RT for 18 hours. The reaction was then quenched with approximately 5-10 mL of water, and the crude product was extracted 3 times with CH<sub>2</sub>Cl<sub>2</sub>. The recovered organic layer was dried over sodium sulfate and concentrated by rotary evaporation to afford 323 mg of (±)-37.4 (84%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.03 (d, J = 7.3 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.43 (m, 2H), 5.18 (sextet, J = 6.4 Hz, 1H), 2.23 (td, J = 7.0, 2.4 Hz, 2H), 1.96 (t, J = 2.5 Hz, 1H), 1.89-1.71 (m, 2H), 1.71-1.55 (m, 2H), 1.35 (d, J = 6.3 Hz, 3H) ppm.<sup>1</sup>

**5,7-dihydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (38.2):**<sup>56</sup>

![Chemical Structure](https://example.com/structure.png)

In a flask, 5.00 g of 38.1 (2,4,6-trihydroxybenzoic acid monohydrate) was dissolved in 40 mL of TFA. To this solution was then added 5 mL of acetone followed by 25 mL of TFAA. The

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<sup>1</sup> Spectral data is in accordance with that reported in ref. 55.
reaction was warmed to RT and stirred for 48 hours. The crude product was then concentrated by rotary evaporation and washed with aqueous sodium bicarbonate. The product was extracted from the aqueous layer with EtOAc, washed with brine, and dried over sodium sulfate. The product was then purified by flash chromatography (EtOAc/hexanes 20-60%) to afford 4.31 g of 38.2, a 77% yield.ii

5,7-dimethoxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (38.3):57

\[
\begin{align*}
\text{38.2} & \xrightarrow{\text{MeI, K}_2\text{CO}_3, \text{acetone, } 0 \, ^\circ \text{C}} \text{38.3}
\end{align*}
\]

In a flask, 200 mg of 38.2 was dissolved in 5.00 mL of acetone. To this solution was then added 789 mg of potassium carbonate, and the solution was stirred at 0 \(^\circ\)C. To the reaction flask was then added 0.36 mL of MeI. The reaction continued stirring at 0 \(^\circ\)C for 24 hours and then determined complete based on the absence of starting material on TLC. The product was poured into 20 mL of water and extracted with EtOAc. The recovered organic layer was washed with brine and dried over sodium sulfate to afford 184 mg of 38.3 without need for further purification, an 81% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.14 (d, \(J = 2.1\) Hz, 1H), 6.07 (d, \(J = 2.2\) Hz, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 1.70 (s, 6H) ppm; \(^{13}\)C NMR (500 MHz, CDCl\(_3\)) \(\delta\) 166.40, 162.80, 159.49, 105.05, 93.76, 93.43, 56.30, 55.68, 25.55 ppm.iii

methyl 2-hydroxy-4,6-dimethoxybenzoate (38.4):58

\[
\begin{align*}
\text{38.3} & \xrightarrow{\text{MeOH, K}_2\text{CO}_3} \text{38.4}
\end{align*}
\]

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ii Spectral data is in accordance with that reported in ref. 56.
iii Spectral data is in accordance with that reported in ref. 57.
In a vial, 200 mg of $38.3$ was dissolved in 3.0 mL of MeOH with stirring at RT. To this vial was then added 232 mg of potassium carbonate. To facilitate dissolution of the potassium carbonate, a minimal amount of water was added. The reaction was stirred at RT for 24 hours, then determined complete by TLC. The solution was acidified with 3.5 mL of 1 M aqueous HCl and extracted with EtOAc. The recovered organic layer was dried over sodium sulfate and filtered, then concentrated by rotary evaporation to yield 168 mg of $38.4$, a 94% yield. $^1$H NMR (500MHz; CDCl$_3$) $\delta$ 12.02 (s, 1H), 6.09 (d, J = 2.4 Hz, 1H), 5.95 (d, J = 2.4 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H) ppm.$^{iv}$

$^{iv}$ Spectral data is in accordance with that reported in ref. 58.
References


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